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Odd protein interaction guides development of olfactory system

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Scientists have discovered a strange mechanism for the development of the fruit fly antennal lobe, an intricate structure that converts the chaotic stew of odors in the environment into discrete signals in the brain.

The fruit fly antennal lobe is analogous to the olfactory bulb in humans.

Researchers at the University of Illinois found that in the fly's antennal lobe a common nervous system receptor actually inhibits the activity of the protein it binds. This is the first time a receptor has been found to behave this way in normal, healthy cells.

The study appears this month in *Nature Neuroscience*.

Receptors and the proteins that bind to them normally work in concert to generate a cascade of changes within cells. A receptor may be embedded in the cell membrane, waiting for a specific protein, called a ligand, to bind to it. Binding often causes the receptor to change its shape, allowing it to interact with other components in the cell. These reactions continue until a specific task is accomplished. Receptors and ligands are fundamental to most chemical signaling in the body, and normally they work together.

The new mechanism, which directs the growth and development of tens of thousands of neurons that are vital to odor detection, instead involves a receptor that disables its protein ligand. The receptor is called "derailed" because its absence causes neurons to grow wildly off-track.

The ligand that binds to the derailed receptor is known as Wnt5 (pronounced “wint 5” – short for “wingless insertion 5”). Both derailed and Wnt5 are known to play key roles in the growth and development of the nervous system.

“In the antennal lobe, derailed is acting as a decoy receptor,” said U. of I. cell and developmental biology professor Huey Hing, who led the study.

“It is nonproductively just sucking up the ligand. Nobody has ever seen a receptor acting in this way. The receptor is actually regulating the ligand.”

The researchers made this discovery when they compared the development of normal antennal lobes to those that formed when Wnt5 or derailed were missing, present at very low levels, or present at extremely high levels.

When Wnt5 was absent, the normally symmetrical odor-sensing structures, called glomeruli, were smaller, malformed, and grew in lopsided positions in the antennal lobes. The commissure, a network of neural fibers that connects the lobes, also was missing.

Because receptors and their ligands normally work together, the researchers expected to see the same problems in the mutant that lacked the derailed receptor. But in these mutants they observed a new phenomenon: Not only were the glomeruli misplaced, they were also growing in the commissure, where they had never been seen before.

“This is when we realized something weird was going on,” Hing said.

This growth of glomeruli in the commissure also occurred when Wnt5 was present at extremely high levels. These observations indicated that the derailed receptors were somehow keeping the Wnt5 protein in check.

When derailed was absent Wnt5 was moving into regions where it didn't belong, and the neural fibers that formed the glomeruli were following. Neural development was truly "derailed."

Further studies determined that supporting cells – not the neurons themselves – were expressing the derailed receptor.

The study reveals an unusual mechanism that is important to the development of the olfactory system, and perhaps to other parts of the nervous system, Hing said. But it also will interest cancer researchers, he said, because the genes that code for the Wnt class of proteins are oncogenes, which sometimes induce the growth of cancer cells.

"Perhaps one day down the road we can make pharmaceutical agents that imitate the role of the derailed receptor," Hing said.

Source: University of Illinois at Urbana-Champaign